Rheumatoid arthritis: predictors of clinical response to TNF blockade
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CHAPTER 8
General discussion and summary
BACKGROUND

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder characterized by synovitis and progressive damage to articular cartilage and subchondral bone in the majority of patients. Besides these well-known effects on the joints, systemic effects may occur like fatigue, low grade fever, malaise, morning stiffness, loss of appetite and weight. All organs can be affected by this disease. In the last years it becomes clear that patients with RA also have an increased cardiovascular (CV) risk which cannot be explained by traditional CV risk factors alone. Systemic inflammation is thought to play a key role in accelerated atherosclerosis. Adipocytokines have provided a plausible link between obesity, inflammation and CV disease. In RA these adipocytokines are increased and are thought to have a role in CV disease. RA is also a well-known risk factor for osteoporosis, not only due to the frequently used glucocorticosteroids (GC) and immobility but also due to increased osteoclastic activation.

The cause of RA is unknown. The combination of genetic susceptibility with environmental inciting events may lead to the development of this disease. In recent years it has become clear that RA is a syndrome compromising several disease subsets, in which different pathogenetic pathways may result in final common pathways associated with persistent synovial inflammation and damage to articular cartilage and underlying bone.

At the end of the last century a new class of drugs, so called biologicals became available for the treatment of RA. Several studies have shown that targeted treatment and intensified treatment especially in early disease may improve outcome quite dramatically. This makes RA anno 2012 a treatable disease. However, remission is induced in only a minority of patients and over time response to biologicals is diminished in a substantial part of RA patients. Thus, there is still a huge unmet need.

TNF blockers are currently often used as a first line biological in light of the vast experience with this class of drugs when DMARD treatment fails. When TNF-blockers fails other targeted treatment, IL-6 receptor antibody (tocilizumab), inhibitor of the co-stimulatory receptors CD80 and CD86-receptors to prevent the interaction between T cells and antigen presenting cells (abatacept) and anti-CD20 antibody (rituximab), are often used. The response to each class of (biological) treatments is quite heterogeneous in RA and the use of these agents is associated with serious side effects in some patients, mainly infectious complications, and considerable costs. Therefore, the prediction of the response to biological treatment in individual patients has become a major clinical challenge in RA to improve cost-effectiveness and reduce unnecessary exposure in patients who are unlikely to respond to a specific mechanism of action. In this thesis we tried to identify clinical parameters or biomarkers that could predict the response to TNF blockade. Conceivably, more effective reduction of inflammation in various subgroups of patients might also translate into reduced CV risk and more effective inhibition of bone loss.

MAIN FINDINGS

Section 1
In the first section we describe studies aimed at the identification of biomarkers predictive of the response to TNF blockade. In the second chapter we examined the value of different
isotypes of RF and ACPA as predictors of response to infliximab in a representative cohort of established RA patients. We found that the presence and the levels of different isotypes of RF and IgM and IgG ACPA were related to clinical response to infliximab at the group level. However, this association was not strong enough to predict response in individual patients when used in isolation. The combination of the presence of different auto-antibodies or isotypes had no additive value in predicting response to infliximab treatment in RA patients. Hence, RF and ACPA isotype levels are statistically associated with response to treatment, but cannot be translated into a predictive test in individual patients yet. Conceivably, prediction might be improved by combination with other molecular and clinical parameters.

A subset of patients with RA exhibits synovial lymphoid neogenesis and in earlier work we found that this is related to increased inflammation25,26. In the third chapter we describe that synovial lymphocyte aggregates are an independent predictor of response in RA patients treated with infliximab. Recently, Wijbrandts et al27 described that synovial TNF levels at baseline partially predicts the clinical response to TNF blockade. When synovial lymphocyte aggregates, disease activity score at baseline, presence of IgG ACPA and expression of synovial TNF were added together in a prediction model, this increased the power to predict the clinical response to infliximab to almost 30%. We also found that a reduction in lymphocyte aggregates after anti-TNF antibody therapy in both RA and psoariatic arthritis patients, which confirms earlier observations that synovial lymphoid neogenesis is associated with inflammation and is reversible.

The E3 ubiquitin ligase synoviolin functions as an anti-apoptotic factor and its expression is associated with arthritis development in mice28. In the fourth chapter we confirm previous work showing over expression of synoviolin in the synovium of RA patients. However, its expression was not specific for RA and also seen in osteoarthritis and psoriatic arthritis patients although expression was lower in these conditions. In contrast to the previously reported association between synoviolin levels in whole peripheral blood and response to anti-TNF treatment29, synovial synoviolin expression was not predictive of later response to TNF blockade. Therefore, the role of synoviolin in the pathogenesis of RA is more complex than previously anticipated and our data do not support the notion that synovial synoviolin levels could be used to improve the prediction of response to anti-TNF treatment.

In the fifth chapter we describe that although infliximab is dosed on body weight, higher body mass index (BMI) index is related to decreased response to infliximab in RA patients suggesting a role for adipose tissue. The baseline BMI showed a positive correlation with the baseline DAS28, indicating a more-active disease in more obese patients. Thus, in spite of the fact that this anti-TNF antibody is dosed per kilogram of body weight, infliximab appears less effective in more obese patients. These results suggest that adipocytokines may have a role in the pathophysiology of RA.

Section 2

In the second part of this thesis we investigated the relationship between adipocytokines, bone mineral density and the response to anti-TNF treatment. There is increasing evidence that adipocytokines may exert pro-inflammatory and destructive effects in RA and also have a role in CV disease in RA patients. In the sixth chapter we describe the effect of TNF blockade and GC on adipocytokines in relation to inflammation, radiological damage and lipid profile in three
cohorts of RA patients. TNF blockade and GC showed opposing effects on vaspin and visfatin serum levels: GC treatment increased vaspin, but not visfatin, while the anti-TNF antibody adalimumab led to decreased visfatin levels without an effect on vaspin levels. The lipid profile improved after adalimumab or long-term low dose GC treatment; in the adalimumab cohort, this was related to a decrease in visfatin levels independent of C-reactive protein (CRP) levels. This suggests a role for visfatin specifically in the improvement of the lipid profile independent of a decrease in disease activity. Of note, visfatin serum levels are independently associated with increased CV disease. The different effect of TNF blockade and GC on visfatin could possibly explain part of the different effects on CV risk profile of these two treatments. Increased vaspin levels are associated with decreased insulin sensitivity, which is commonly seen after GC treatment. Vaspin could, therefore, also be involved in the opposing effects of anti-TNF and GC treatments on CVD risk. After several months of treatment with adalimumab or GC, we observed a decline in resistin levels, associated with a decrease in DAS28, CRP and erythrocyte sedimentation rate (ESR), or ESR only, respectively. In the adalimumab cohort, serum resistin levels at baseline were predictive of radiological damage at baseline, independent of ACPA status or CRP. These data further support an important patho-physiological role for resistin and visfatin in RA.

Due to systemic inflammation osteoporosis is more frequent in RA patients and in the seventh chapter we describe that anti-TNF therapy may arrest bone loss in the lumbar spine and femur neck in patients with RA. This is in contrast with the progressive bone loss observed after conventional DMARD therapy. Of interest, a beneficial effect of low dose prednisone on the change in femur neck BMD was also observed with a relative increase with prednisone use compared to no concomitant prednisone use after one year. Consistent with previous observations, the data also suggest that the net effect of low-dose GC on bone mineral density in RA may be beneficial, possibly resulting from their anti-inflammatory effects.

CONCLUSION

It may be difficult to identify a single biomarker that can be used to predict the response to anti-TNF therapy in the context of individualized health care. We have however generated evidence that certain biomarkers can be identified, which are predictive on the group level. Based on insights derived from these studies, existing treatment algorithms may be further refined46. In addition to the need for identification of novel biomarkers beyond the scope of the studies described in this thesis, combination of multiple markers may bear most promise to further improve the performance of a biomarker-guided approach.

REFERENCE LIST
